BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PATENT SPECIFICATION

746,016

Date of Application and filing Complete Specification: June 24, 1952.
No. 27388/54.
Application made in United States of America on Oct. 1, 1951.
Application made in United States of America on Oct. 1, 1951.
(Divided out of No. 745,900).
Complete Specification Published: March 7, 1956.

Index at acceptance:—Class 2(3), C2D(6:19).

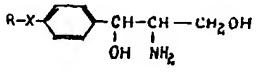
COMPLETE SPECIFICATION

Amino Diol Compounds and method for preparing same

We, STERLING DRUG INC., a corporation organised under the laws of the State of Delaware, United States of America, of 1450 Broadway, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new chemical compounds and the preparation thereof, said compounds being useful as intermediates for the production of other chemical compounds as hereinafter described.

More particularly, this invention relates to new compounds having the formula

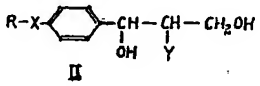


I

where R is a hydrocarbon radical having 1—7 carbon atoms, and X is S or SO_2. The hydrocarbon radical R includes aliphatic, cycloaliphatic, aryl, and benzyl radicals having 1—7 carbon atoms and represents, for example: branched and unbranched alkyl radicals, such as methyl, ethyl, n-propyl, n-butyl, isobutyl, n-heptyl, isoamyl; alkenyl radicals, such as allyl, methallyl; cycloalkyl radicals, such as cyclohexyl, cyclopentyl; benzyl; phenyl; and ortho-, meta- and para-tolyl radicals.

This application is a divisional of Appln. 15864/52 (Serial No. 745,900) and types of compounds embraced by the generic formula hereinabove are set out in that application.

The amines of the present invention are prepared by deacylating the 2-(aliphatic carboxylic acylamino)-1-(4-hydrocarbonylmercapto- (or sulfonyl) phenyl)-1,3-propanediols of the aforesaid parent application. The latter compounds (having the formula II below) are readily deacylated by treatment with hot mineral acids to yield the corresponding free amines having the formula I above,



II

where R and X have the same significance as in formula I above and Y is an aliphatic carboxylic acylamino radical.

These novel amines I are readily acylated to yield acylamino derivatives and if desired can be readily reconverted to the aliphatic carboxylic acylamino derivatives II. The amines I react with organic and inorganic acids to form salts. When the acylamino compounds of Appln. 15864/52 (Serial No. 745,900) wherein the acylamino group is other than acetylamino are desired, it is generally advantageous to prepare them by acylating the appropriate 2-amino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol of the present invention which has been obtained by hydrolysis of the corresponding 2-acetylamino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol. This is described in the aforesaid application.

Moreover the 2-amino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols of the present invention are utilizable as intermediates in the production of the 2-amino-1-(4-hydrocarbonylsulfonylphenyl)-1,3-propanediols.

It will be appreciated that in preparing the 2-aliphatic carboxylic acylamino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediols of the aforesaid parent application using racemic or optically inactive intermediates, the final products will of course be obtained in a racemic or optically inactive form. When it is desired to obtain the optically active forms of the acylaminodiols, we have found that it is generally most convenient to acylate the appropriate optically active 2-amino-1-(4-hydro-

carbonylmercaptophenyl) - 1,3 - propanediol (derived by resolution of the racemic aminodiol) by treatment with an aliphatic carboxylic acyl chloride, anhydride, or lower alkyl ester as set forth in the parent application.

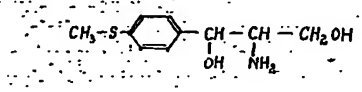
It will also be appreciated that when a racemic or optically inactive form of the 2-aliphatic carboxylic acylamino-1-(4-hydrocarbonylmercaptophenyl)-1,3-propanediol is employed as the starting material in the oxidation process of the parent application, there will of course be obtained a racemic form of the 2-aliphatic carboxylic acylamino-1-(4-hydrocarbonylsulfonylphenyl) - 1,3 - propanediol. On the other hand, when an optically active form of the starting material is employed in that process, the product will likewise be optically active. The optically active forms of the products of the present invention are readily obtained as follows:- A racemic form of the acylamino-compound is deacylated by treatment with a hot mineral acid to yield a racemic form of 2-amino-1-(4-hydrocarbonyl-mercaptophenyl)-1,3-propanediol which is resolved through use of an optically active organic acid. The optically active forms of the amines thus obtained may then be treated with an aliphatic carboxylic acylating agent to yield the desired optically active forms of the acylamino-compound.

The invention is illustrated by the following examples without, however, being limited thereto.

EXAMPLE 1.

2-Amino-1-(4-methylmercaptophenyl)-1,3-propanediol.

A mixture of 50 parts by weight of racemic 2-acetylamino - 1 - (4-methylmercaptophenyl)-1,3-propanediol, 100 parts by weight of concentrated hydrochloric acid, and 500 parts by weight of water was warmed on a steam bath for thirty minutes. The resulting solution was cooled to about 40° C. and was then made strongly alkaline by addition of 35% aqueous sodium hydroxide solution. The alkaline solution was then refrigerated. The white solid which separated from the cooled solution was collected on a filter. There was thus obtained 27 parts by weight of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol, having the formula



This product melted at 130.7—131.9° C. after recrystallization from methanol.

A solution of 17.5 g. of the 2-amino-1-(4-methylmercaptophenyl) - 1,3 - propanediol described above, which of course was a racemic or optically inactive form of the compound, in 100 ml. of methanol and a solution of 13 g. of *d*-tartaric acid in 100 ml. of methanol were mixed and the mixture was allowed to stand at 15—20° C. for about six hours. The solid which had separated from the solution during this period was then collected on a filter, the methanolic filtrate being retained for treatment as described below. There was thus obtained 18 g. of solid which melted at 190—196° C. This solid was suspended in 150 ml. of water and sufficient dilute hydrochloric acid was added to effect solution of the solid. To the solution thus obtained there was added 50 ml. of 35% aqueous sodium hydroxide solution which caused the separation of 11.7 g. of yellowish solid from solution. This solid melted at 127—135° C. Two recrystallizations of this product from methanol yielded 1.5 g. of coarse white needles which melted at 152—153° C. This product was a levo-rotary form of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol having $[\alpha]_D^{23} = -21°$ (1% solution in 95% ethanol).

The methanolic filtrate retained above was distilled on the steam bath to remove the methanol. The residue thus obtained was dissolved in 50 ml. of water and the resulting solution was treated with 15 ml. of 35% caustic solution. This caused the separation of 3.0 g. of white solid which melted at 141—150° C. This product was recrystallized twice from methanol, thus yielding 1.0 g. of white crystals consisting of a dextro-rotary form of 2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol which melted at 152—153° C. and had $[\alpha]_D^{23} = +21°$ (1% solution in 95% ethanol).

The racemic amine was also resolved in the following manner: 33.0 g. of racemic 2-amino-1 - (4-methylmercaptophenyl)-1,3-propanediol and 34.6 g. of *d*-N-benzoylthreonine (m.p. 149 151° C.; obtained by benzoylation of *d*-threonine) were dissolved in 500 ml. of methanol by warming. Crystallization was initiated by cooling the solution to 25° C. and scratching the inner walls of the container. The solution was refrigerated at 5° C. for about ten hours and then the crystals which had separated from solution were collected on a filter, the filtrate (A) being retained for recovery of the dextro-rotary amine as described below. The solid on the filter was washed with a few ml. of cold methanol and dried at 70° C. There was thus obtained 31.3 g. of levo-rotary-2-amino-1-(4-methylmercaptophenyl)-1,3-propanediol *d*-N-benzoylthreonine salt which melted at 184—186° C. This crop of salt was dissolved in 100 ml. of water containing 6.2 ml. of concentrated hydrochloric acid and the solution was then made alkaline by addition of 13 ml. of 35% aqueous sodium hydroxide solution. 20 g. of sodium chloride was dissolved in this solution which was then cooled to 5° C. A heavy crop of crystals separated from the solution and this solid was collected on a filter.

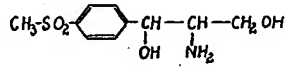
washed with a little saturated aqueous sodium chloride solution and dried at 70° C. There was thus obtained 15.0 g. of crude levo-rotary 2 - amino-1-(4-methylmercaptophenyl) - 1,3-propanediol which melted at 147—150° C. This product was recrystallized from 150 ml. of methanol to yield 11.9 g. of the pure levo-rotary amine which melted at 151—153° C. By concentrating the mother liquor, 3.0 g. of solid consisting largely of the racemic amine was recovered.

The filtrate (A) retained as indicated above was evaporated at reduced pressure. The residue thus obtained was dissolved in 100 ml. of water containing 62 ml. of concentrated hydrochloric acid and the solution was made alkaline by addition of 13 ml. of 35% aqueous sodium hydroxide solution. 20 g. of sodium chloride was dissolved in this solution which was then cooled to 5° C. The heavy crop of crystalline solid which separated from the solution was collected on a filter, washed with a few ml. of saturated aqueous sodium chloride solution and dried at 70° C. There was thus obtained 13.5 g. of crude dextro-rotary 2-amino - 1 - (4 - methylmercaptophenyl)-1,3-propanediol. This product was recrystallized from methanol to yield 8.5 g. of the pure dextro-rotary amine which melted at 151—153° C. By concentrating the mother liquor, 5.0 g. of solid consisting largely of the racemic amine was recovered.

EXAMPLE 2.

2-Amino-1-(4-methylsulfonylphenyl)-1,3-propanediol.

A mixture of 5 g. of the dextro-rotary 2-dichloroacetylamino - 1 - (4 - methylsulfonylphenyl)-1,3-propanediol, 9 ml. of concentrated hydrochloric acid, and 40 ml. of water was heated on a steam bath for one hour. The water was removed from the resulting solution by distillation *in vacuo* to give a light yellow residual syrup which solidified on standing at room temperature (*circa* 25° C.) for several days. This solid was heated to 60—70° C. with 20 ml. of saturated aqueous sodium chloride solution until all dissolved. The resulting solution was treated with 3.5 ml. of 35% aqueous sodium hydroxide solution and extracted while still warm with approximately 100 ml. of n-butanol. On cooling and standing, 0.9 g. of white crystals separated from the butanol extract. This product, which was levo-rotary 2 - amino - 1-(4-methylsulfonylphenyl)-1,3-propane-diol, having the formula



melted at 141.4—142.6° C. and had $[\alpha]_D^{25} = -19.8°$ (1% solution in 95% ethanol). This water-soluble base formed a water-soluble hydrochloride which melted at 200.4—202.6° C. and had $[\alpha]_D^{25} = -26.0°$ (1% solution in 95% alcohol).

In analogous fashion, when the levo-rotary and the racemic 2-dichloroacetylamino-1-(4-methylsulfonylphenyl) - 1,3-propanediols are deacylated by treatment with concentrated hydrochloric acid, there are obtained the dextro-rotary and the racemic 2-amino-1-(4-methylsulfonylphenyl) - 1,3-propanediols, respectively.

It is to be understood that all acylamino-diols and aminodiols referred to throughout the specification are threo forms.

What we claim is:—

1. A process for preparing threo amino diol compounds of the formula I herein, which comprises deacylating a threo compound of the formula II herein.

2. A process according to claim 1, in which the compound of formula II is treated with a hot mineral acid.

3. A process according to claim 1 or 2, in which R in the formulæ is alkyl, e.g. methyl.

4. The processes of preparing threo amino diol compounds of the formula I herein, substantially as set forth in the Examples.

5. Threo amino diol compounds of the formula I herein, whenever prepared by a process according to any one of the preceding claims.

6. A threo amino diol compound of the formula I herein.

7. A compound according to claim 6, in which R in the formula is alkyl, e.g. methyl.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1956.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

Amino diol compounds and method for preparing same

Patent Number: GB746016
Publication date: 1956-03-07
Inventor(s):
Applicant(s): STERLING DRUG INC
Requested Patent: GB746016
Application Number: GB19540027388 19520624
Priority Number(s): USX746016 19511001
IPC Classification:
EC Classification:
Equivalents:

Abstract

The invention comprises threo aminodiol compounds of the general formula (wherein R represents a hydrocarbon radical of 1-7 carbon atoms and X represents S or SO2), and the preparation thereof by deacylating their N-acyl derivatives (the acyl group being the residue of an aliphatic carboxylic acid), e.g. by treatment with hot mineral acid. The products form salts with organic and inorganic acids, and their racemic forms may be resolved into optically active forms by means of optically active organic acids. In examples (1) dl-threo2 - acetylamino - 1 - (p - methylmercaptophenyl) - 1:3 - propanediol is heated with dilute hydrochloric acid, and the resulting dlthreo - 2 - amino - 1 - (p- methylmercaptophenyl) - 1:3 - propanediol is resolved with the aid of d - tartaric acid or d - N - benzoylthreonine; (2) (+) -, (-) - or racemic - threo2 - dichloroacetylamino - 1 - (p - methylsulphonylphenyl) - 1:3 - propanediol is hydrolysed as in (1) to (-) -, (+) - or racemicthreo - 2 - amino - 1 - (p - methylsulphonylphenyl)-1:3-propanediol.